IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Clifford J. Herman
Serial No.: 10/554,133
Filed: October 20, 2005
Confirmation No.: 9352
For: METHYLPHENIDATE SOLUTION AND ASSOCIATED METHODS OF ADMINISTRATION AND PRODUCTION
Examiner: Deirdre Renee Claytor

Art Unit: 1617

December 4, 2009

Declaration of Inventor Clifford J. Herman

I, Clifford J. Herman, declare as follows:

1. I am the sole inventor of the subject matter claimed in the above-entitled United States patent application, Serial Number 10/554,133.

2. I have reviewed the final Office action issued June 5, 2009 on the present application, the Midha et al. (U.S. Patent No. 6,127,385) and Epstein et al. (U.S. Patent Application Publication No. 2002/0103162) references cited therein, and the pending claims (claims 1-23) of the present application.

3. I have also reviewed my previous Declaration of February 5, 2008. As stated therein, the following is to be noted:

(a) The present invention is directed to a storage stable methylphenidate solution (e.g., a solution of the free base or a pharmaceutically acceptable salt thereof) that has improved chemical stability, and therefore improved storage stability or shelf-life as well. As noted in the present application, I have discovered that by preparing a solution of methylphenidate using a solvent system comprising a combination of water and a non-aqueous solvent, and in particular, a solvent system comprising less than about 50% water (or alternatively greater than about 50% of the non-aqueous solvent), the chemical stability, and therefore the storage stability or shelf-life, of the solution is improved.

(b) Neither Midha et al. nor Epstein et al., alone or in combination, disclose or suggest a storage stable solution comprising methylphenidate, or methylphenidate HCl, and a solvent system that has a water concentration of less than 50%.

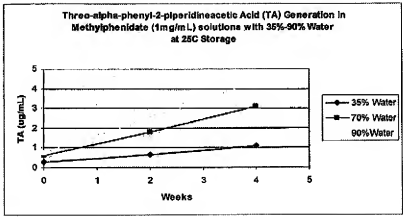
(c) Neither Midha et al. nor Epstein et al. recognize or acknowledge that methylphenidate solutions are inherently unstable. As a result, neither of the cited references provides motivation to modify the solutions generally disclosed therein, in order to achieve a storage stable methylphenidate solution that includes less than about 50% water.

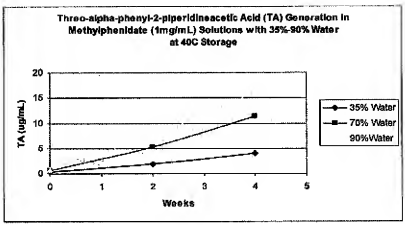
(d) Additionally, both of the cited references fail to recognize the added benefit of including a given concentration (e.g., from about 0.5 mg/ml to about 5.0 mg/ml) of an organic acid (e.g., citric acid) in a solution comprising methylphenidate, or methylphenidate HCl, and a solvent system that has a water concentration of less than 50%, in order to further stabilize the solution. Although Epstein et al. list citric acid as a metal chelating agent, they fail to recognize the use of citric acid, or any organic acid, as a stabilizing agent. Thus, there is also no recognition to use an organic acid in the recited amounts.

4. To illustrate the improved stability achieved in a solution comprising methylphenidate, or methylphenidate HCl, and a solvent system that has a water concentration of less than 50%, as compared to similarly prepared solutions that have a water content of greater than 50%, stability tests were conducted under my direction consistent with Example 1 of the present application. Specifically, stock solutions were prepared having a methylphenidate concentration of either 1 mg/ml or 2 mg/ml, and a citric acid concentration of 2.5 mg/ml, in a mixed solvent system having a water content of either 35%, 70% or 90%. Samples of these stock solutions were then stored for a period of 4 weeks at 25°C and 60% relative humidity, or 40°C and 75% relative humidity. Aliquots of these stored solutions were taken at 2 weeks and 4 weeks, and analyzed for threo-alpha-phenyl-2-piperidine acetic acid (TA), because the primary route of methylphenidate HCl degradation in solution is hydrolysis that results in the formation of TA.

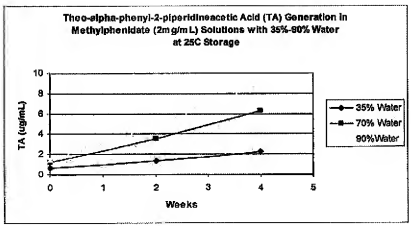
5. The results of these stability tests, which are provided in the graphs below, show that under both storage conditions (i.e., both sets of temperature and relative humidity conditions), the sample solutions prepared in a solvent system having a water content of greater than 50% consistently contained significantly more TA, and thus were significantly less stable, than the sample solutions prepared in a solvent system having a water content of less than 50%. Specifically, the graphs show that the sample solutions prepared in a solvent system having a water content of 70% contained approximately three times more TA after 4 weeks of storage than the sample solutions prepared in a solvent system having a water content of 35%. The graphs also show that the sample solutions prepared in a solvent system having a water content of 90% contained approximately four times more TA after 4 weeks of storage than the sample solutions prepared in a solvent system having a water content of 35%.

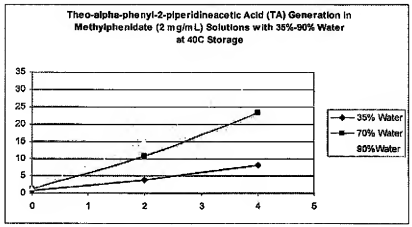
Results of 1 mg/ml Samples:





Results of 2 mg/ml Samples:





6. To illustrate the improved stability achieved in a solution comprising methylphenidate, or methylphenidate HCl, a solvent system that has a water concentration of less than 50%, and an organic acid within a concentration in the range of about 0.5 mg/ml to about 5.0 mg/ml (as recited in claims 2 and 9), or about 0.5 mg/ml to about 3.0 mg/ml (as recited in claim 14), as compared to similarly prepared solutions that have an organic acid concentration outside the recited range, additional stability tests were conducted under my direction consistent with Example 1 of the present application. Specifically, stock solutions were prepared having a methylphenidate concentration of either 1 mg/ml or 2 mg/ml, a mixed solvent system having a water content of 35%, and a citric acid concentration of either 0.25 mg/ml, 2.5 mg/ml, or 7.5 mg/ml. Samples of these stock solutions were then stored for a period of 4 weeks at 40°C and 75% relative humidity. Aliquots of these stored solutions were taken after 4 weeks and analyzed for threo-alpha-phenyl-2-piperidine acetic acid (TA).

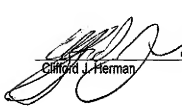
7. The results of these stability tests, which are provided in the table below, show that the sample solutions prepared having a citric acid content of either 0.25 mg/ml or 7.5 mg/ml consistently contained between approximately 30% and 60% more TA, and thus were significantly less stable, than the sample solutions prepared having a citric acid content of 2.5 mg/ml.

Citric Acid	TA Generation after 4 Weeks at 40°C/75% RH (µg/ml)	
	1 mg/ml methylphenidate solution	2 mg/ml methylphenidate solution
0.25 mg/ml	5.52	10.28
2.5 mg/ml	4.04	8.06
7.5 mg/ml	6.35	12.91

8. For foregoing reasons, as well as for those set forth in my Declaration of February 5, 2008, the Midha et al. and Epstein et al. references do not disclose or suggest preparing a storage stable solution of

methylphenidate using a solvent system comprising a combination of less than about 50% water and greater than about 50% of a non-aqueous solvent. They also do not disclose or suggest such a solution that additionally includes a given concentration of at least one organic acid, as required by the claims of the present application.

9. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.



Clifford J. Herman

12.3.09
Date